PCT/EP 97/07011

60/032864

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UNITED STATES DEPARTMENT OF COMMERCE
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PRIORITY DOCUMENT

January 8, 1998

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/032,864*
FILING DATE: *December 13, 1996*

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COMMISSIONER OF PATENTS AND TRADEMARKS

P. R. Grant

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Certifying Officer

PATENT APPLICATION SERIAL NO. 60/032864

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

010 UT 01/30/97 60032864
1 114 150.00 CK 573.0P

PTO-1556
(5/87)

FORM 23-1.1

60/032864

MAIL ROOM DEC 13 1996 62 PAT. & TRADEMARK OFF.

Appendix A

PTO/SB/16 (6-95)
Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

## PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

| Docket Number | 573.0P | Type a plus sign (+) inside this box → | + |
|---|---|---|---|

INVENTOR(s)/APPLICANT(s)

| | LAST NAME | FIRST NAME | MIDDLE INITIAL | RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY) |
|---|---|---|---|---|
| 1-CR | Nicolaou | Kyriacos | C. | La Jolla, California CA |
| 2-CR | Sarabia | Francisco | | La Jolla, California CA |
| 3-CR | Ninkovic | Sacha | | San Diego, California CA |

additional name are attached

TITLE OF THE INVENTION (280 characters max)

SYNTHETIC APPROACHES FOR EPOTHILONE A AND RELATED ANALOGS

CORRESPONDENCE ADDRESS

THE SCRIPPS RESEARCH INSTITUTE, Office of Patent Counsel
10550 North Torrey Pines Road, TPC-8, La Jolla

| STATE | CA | ZIP CODE | 92037 | COUNTRY | United States |
|---|---|---|---|---|---|

ENCLOSED APPLICATION PARTS (check all that apply)

- [X] Specification — Number of Pages: 24
- [X] Drawing(s) — Number of Sheets: 7
- [ ] Small Entity Statement
- [ ] Other (specify)

METHOD OF PAYMENT (check one)

- [X] A check or money order is enclosed to cover the Provisional filing fees
- [ ] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number:

PROVISIONAL FILING FEE AMOUNT ($): 150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- [ ] No.
- [X] Yes, the name of the U.S. Government agency and the Government contract number are: NIH CA58336

Respectfully submitted,

SIGNATURE [signature] Date 12/13/96

TYPED or PRINTED NAME Donald G. Lewis

REGISTRATION NO. (if appropriate) 28,636

[X] Additional inventors are being named on separately numbered sheets attached hereto

## PROVISIONAL APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistant Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Continuation of Appendix A (additional inventors)

| | |
|---|---|
| Yang, Zhen | San Diego, California |
| He, Yun | San Diego, California |
| Vourloumis, Dionisios | San Diego, California |
| Vallberg, Hans | San Diego, California |

Page 2 of 2

FORM 23-1



60/032864

Attorney's Docket No. 573.0P

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: K.C. Nicolaou, Francisco Sarabia, Sacha Ninkovic, Zhen Yang, Yun He, Dionisios Vourloumis, Hans Vallberg

For: SYNTHETIC APPROACHES FOR EPOTHILONE A AND RELATED ANALOGS

Box Provisional Patent Application
Commissioner of Patents and Trademarks
Washington, D.C. 20231

# COVER SHEET FOR FILING PROVISIONAL APPLICATION
(37 C.F.R. § 1.51(2)(i))

WARNING: *"A provisional application must also include a cover sheet identifying the application as a provisional application. Otherwise, the application will be treated as an application filed under § 1.53(b)(1)." 37 C.F.R. § 1.53(b)(2)(i).*

NOTE: *"A complete provisional application does not require claims since no examination on the merits will be given to a provisional application. However, provisional applications may be filed with one or more claims as part of the application. Nevertheless, no additional claim fee or multiple dependent claims fee will be required in a provisional application." Notice of December 5, 1994, 59 FR 63951, at 63953.*

*"Any claim filed with a provisional application will, of course, be considered part of the original provisional application disclosure." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

NOTE: *"A provisional application shall not be entitled to the right of priority under § 1.55 or 35 U.S.C. 119 or 365(a) or to the benefit of an earlier filing date under § 1.78 or 35 U.S.C. 120, 121 or 365(c) of any other application." 37 C.F.R. § 1.53(b)(2)(iii).*

NOTE: *"No information disclosure statement may be filed in a provisional application." 37 C.F.R. § 1.51(2)(b). "Any information disclosure statements filed in a provisional application would either be returned or disposed of at the convenience of the Office." Notice of December 5, 1994, 59 FR 63591, at 63594.*

NOTE: *"No amendment other than to make the provisional application comply with all applicable regulations, may be made to the provisional application after the filing date of the provisional application." 37 C.F.R. § 1.53(b)(2).*

---

**CERTIFICATION UNDER 37 CFR 1.10**

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on December 13, 1996 (date), in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. 1.10, Mailing Label Number EM512698968US addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Paul K. Richter
Signature

Paul K. Richter
(type or print name of person certifying)

NOTE: *Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. (37 C.F.R. 1.10(b))*

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 CFR 1.8(a) cannot be used to obtain a date of mailing or transmission for this correspondence. 37 C.F.R. 1.8(a)(i)(A).*

WARNING: A provis[illegible] application may be abandoned by operation of 3[illegible] [illegible].C. 111(b)(5) on a Saturday, Sunday, [illegible] ederal holiday within the District of Columbia. [illegible] ich case, a nonprovisional application claiming benefit of the provisional application under 35 U.S.C. 119(e) must be filed no later than the preceding day that is not a Saturday, Sunday, or Federal holiday within the District of Columbia. Notice of April 14, 1995, 60 Fed. Reg. 20,195 at 20,202.

1. The accompanying application is a provisional application. (37 C.F.R. § 1.51(a)(2)(i)(A))

2. The name(s) of the inventor(s) is/are (37 C.F.R. § 1.51(a)(2)(i)(B)):

NOTE: *While the name or names of the inventors are required in order to accord a provisional application a filing date, a provisional application is not required to be signed by the inventor or the assignee. No oath or declaration is required. Presumably, most provisional applications will be filed by a registered practitioner without a power of attorney being filed. Notice of December 5, 1994, 59 FR 63591, at 63594.*

NOTE: *"The naming of inventors for obtaining a filing date for a provisional application is the same as for other applications. A provisional application filed with the inventors identified as 'Jones et al.' will not be accorded a filing date earlier than the date upon which the name of each inventor is supplied unless a petition with the fee set forth in § 1.17(i) is filed which sets forth the reasons the delay in supplying the names should be excused. Administrative oversight is an acceptable reason. It should be noted that for a 35 U.S.C. 111(a) application to be entitled to claim the benefit of the filing date of a provisional application the 35 U.S.C. 111(a)[,] application must have at least one inventor in common with the provisional application." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

*The term "invention" is typically used to refer to subject matter which applicant is claiming in his/her application. Because claims are not required in a provisional application, it would not be appropriate to reference joint inventors as those who have made a contribution to the "invention" disclosed in the provisional application. If the "invention" has not been determined in the provisional application because no claims have been presented, then the name(s) of those person(s) who have made a contribution to the subject matter disclosed in the provisional application should be submitted. Section 1.45(c) states that "if multiple inventors are named in a provisional application, each named inventor must have made a contribution, individually or jointly, to the subject matter disclosed in the provisional application." All that § 1.45(c) requires is that if someone is named as an inventor, that person must have made a contribution to the subject matter disclosed in the provisional application. When applicant has determined what the invention is by the filing of the 35 U.S.C. 111(a) application, that is the time when the correct inventors must be named. The 35 U.S.C. 111(a) application must have an inventor in common with the provisional application in order for the 35 U.S.C. 111(a) application to be entitled to claim the benefit of the provisional application under 35 U.S.C. 119(e). Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,208.*

*"If all the names of the actual inventor or inventors are not supplied when the specification and any required drawings are filed, the provisional application will not be given a filing date earlier than the date upon which the names are supplied unless a petition, with the fee set forth in § 1.17(q), is filed, which sets forth that the reasons for the delay in supplying the names should be excused." 37 C.F.R. § 1.53(b)(2).*

| | (GIVEN NAME) | (MIDDLE INITIAL OR NAME) | (FAMILY (OR LAST) NAME) |
|---|---|---|---|
| 1. | Kyriacos | C. | Nicolaou |
| 2. | Francisco | | Sarabia |
| 3. | Sacha | | Ninkovic |

Additional names are listed on accompany sheet

(Cover Sheet for Filing Provisional Application [23-1]—page 2 of 6

3. Address(es) of the inventor(s), as numbered above (37 C.F.R. § 1.51(a)(2)(i)(C)):
   1. 9625 Blackgold Road, La Jolla, California 92037
   2. 3116 Via Alicante Dr., Apt. G, La Jolla, California 92037
   3. 3855 Novel Drive, Apt. 2216, San Diego, California 92122

   Additional address are listed on accompanying sheet
4. The title of the invention is (37 C.F.R. § 1.51(a)(2)(i)(D)):

   SYNTHETIC APPROACHES FOR EPOTHILONE A AND RELATED ANALOGS
5. The name, registration, and telephone number of the attorney *(if applicable)* is (37 C.F.R. § 1.51(a)(2)(i)(E)):

   Name of attorney: Donald G. Lewis

   Reg. No. 28,636 Tel. ( 619 ) 678-2937

   *(complete the following, if applicable)*

   ☐ A power of attorney accompanies this cover sheet.
6. The docket number used to identify this application is (37 C.F.R. § 1.51(a)(2)(i)(F)):

   Docket No.: 573.0P
7. The correspondence address for this application is (37 C.F.R. § 1.51(a)(2)(i)(G)):

   THE SCRIPPS RESEARCH INSTITUTE, Office of Patent Counsel

   10550 North Torrey Pines Road, TPC-8, La Jolla, CA 92037
8. Statement as to whether invention was made by an agency of the U.S. Government or under contract with an agency of the U.S. Government. (37 C.F.R. § 1.51(a)(2)(i)(H)).

This invention was made by an agency of the United States Government or under contract with an agency of the United States Government.

☐ No.

☒ Yes.

The name of the U.S. Government agency and the Government contract number are:

NIH CA58336

9. Identification of documents accompanying this cover sheet:

A. Documents required by 37 C.F.R. §§ (a)(2)(ii)–(iii):

Specification: No. of pages 24

Drawings: No. of sheets 7

B. Additional documents:

☐ Claims: No. of claims ______

*Note: A complete provisional application does not require claims. 37 C.F.R. § 1.51(a)(2).*

☐ Power of attorney

☐ Small entity statement

☐ Assignment

☐ Other

*NOTE: Provisional applications may be filed in a language other than English as set forth in existing § 1.52(d). However, an English language translation is necessary for security screening purposes. Therefore, the PTO will require the English language translation and payment of the fee mandated in § 1.52(d) in the provisional application. Failure to timely submit the translation in response to a PTO requirement will result in the abandonment of the provisional application. If a 35 U.S.C. 111(a) application is filed without providing the English language translation in the provisional application, the English language translation will be required to be supplied in every 34 U.S.C. 111(a) application claiming priority of the non-English language provisional application. Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

10. Fee

The filing fee for this provisional application, as set in 37 C.F.R. § 1.16(k), is $150.00, for other than a small entity, and $75.00 for a small entity.

☐ Applicant is a small entity.

*NOTE: "A verified statement in compliance with existing § 1.27 is required to be filed in each provisional application in which it is desired to pay reduced fees." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,197.*

11. Small entity statement

☐ The verified statement(s) that this is a filing by a small entity under 37 C.F.R. §§ 1.9 and 1.27 is(are) attached.

12. Fee payment being made at this time

☐ Not enclosed

☐ No filing fee is to be paid at this time (This and the surcharge required by 37 C.F.R. § 1.16(l) can be paid subsequently).

☒ Enclosed

Total fee enclosed $ 150.00

13. Method of fee payment

☒ Check in the amount of $ 150.00

☐ Charge Account No. ______
in the amount of $ ______

A duplicate of this Cover Sheet is attached.

Please charge Account No. 19-0962 for any fee deficiency.

Date: ______

Tel.: (    )

______
Signature of submitter

OR

______
Signature of attorney

Date: 12/13/96

Reg. No.: 28,636

Tel.: (619) 784-2937

Donald G. Lewis
(type or print name of attorney)

THE SCRIPPS RESEARCH INSTITUTE
10550 N. Torrey Pines Road
P.O. Address

La Jolla, CA 92037

Names and addresses of additional inventors:

| | |
|---|---|
| 4. Zhen Yang | 4158 Decoro Street, No. 2, San Diego, CA 92122 |
| 5. Yun He | 9605 Genesee Avenue, No. H2, San Diego, CA 92122 |
| 6. Dionisios Vourloumis | 4249 Nobel Drive, Apt. 39, San Diego, CA 92122 |
| 7. Hans Vallberg | 4249 Novel Drive, Apt. 39, San Diego, CA 92122 |

# Total Synthesis of Epothilone A: The Olefin Metathesis Approach†

† This paper is dedicated to Professor Thomas J. Katz on the occassion of his 60th birthday and in recognition of his pioneering studies on the olefin metathesis reaction.

Zhen Yang, Yun He, Dionisios Vourloumis, Hans Vallberg, K. C. Nicolaou*

[*] Prof. Dr. K.C. Nicolaou, Y. He, Drs. D. Vourloumis, H. Vallberg, Z. Yang
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[**] This work was financially supported by The Skaggs Institute of Chemical Biology and the National Institutes of Health (USA).

ted Keywords: epothilone, total synthesis, olefin metathesis

ted **Table Content Text**

The total synthesis of the antitumor agent epothilone A has been achieved by a highly convergent and flexible strategy involving olefin metathesis as a key step to form the macrocyclic skeleton of the target molecule. The strategy may allow the chemical synthesis of a library of designed epothilones for biological screening.

Epothilone A (1)[1,2] is an exciting new natural product, isolated from the myxobacteria *Sorangium cellulosum* strain 90, with novel molecular architecture, important biological properties and intriguing mechanism of action. Amongst its biological properties are potent antifungal and selective cytotoxic activities.[1-4] Its mechanism of action against tumor cells has been attributed to binding and stabilization of microtubules[4], resembling in that respect, taxol.[5] Following our recent report[6] on an olefin metathesis[7] based approach towards this class of compounds, we now wish to disclose the total synthesis of epothilone A (1) by this novel strategy.

Figure 1 shows the strategic bond disconnections that led to the convergent strategy utilized in this synthesis. As one can surmise by inspection of Figure 1, the plan calls for the construction of the three key building blocks **5**, **6** and **10** (Scheme 1), their union and elaboration to the 16-membered macrocycle and final epoxidation. For the present approach, the olefin metathesis step and the selective epoxidation of the $\Delta^{12,13}$-double bond in the final step were considered, at the outset, both risky and crucial.

Scheme 1 summarizes the construction of the key building blocks **5**, **6** and **10**. Thus, the synthesis of the requisite carboxylic acid **5** commenced with the known ketoaldehyde **2**[8] which reacted selectively with Brown's allyl isopinocampheyl borane reagent [(+)-$Ipc_2B$(allyl)][9] in ether at -100 °C to afford alcohol **3**[10] in 74% yield. Protection of this alcohol with TBSOTf-2,6-lutidine led to the silyl ether **4** in 98% yield. Ozonolytic cleavage of the double bond in the latter compound, followed by $NaClO_2$ oxidation of the resulting aldehyde gave the targeted carboxylic acid **5** in 75% yield. *overall was de
The preparation of the heterocyclic component **10** was carried out from the known thiazole ester **7**[11] by: a) reduction to the corresponding aldehyde (**8**) (Dibal-H, 90% yield); b) Wittig reaction with $Ph_3P$=C(Me)CHO to afford the conjugated aldehyde **9** (90% yield); and c) condensation of **9** with (+)-$Ipc_2B$(allyl) in ether at -100 °C (96% yield).[10]

Having secured the requisite building blocks, we then turned our attention to their coupling and further elaboration. Scheme 2 depicts these final stages of the present total synthesis of epothilone A (1). Thus, condensation of the dianion of 5 (2.2 equiv. of LDA, THF, -78 to -40 °C) with aldehyde 6[6,12] (1.2 equiv) at -78 to -40 °C resulted in the formation of the desired aldol product (11) as the major isomer, together 7R with its ~~6R,7S~~ diastereomer in high yield and *ca* 2:1 ratio. Esterification of this mixture with the hydroxy component 10 (2.0 equiv) proceeded in the presence of DCC and 4-DMAP in toluene at 25 °C to afford compound 12 and its 6S,7R ~~6R,7S~~ diastereomer in 70% overall total yield[13] from ketoacid 5. The two isomers were chromatographically separated [silica gel, ethyl acetate:hexane (1:5), $R_f$ = 0.29 (12, 45% overall yield from 5), 0.24 (6S,7R ~~6R,7S~~ diastereomer of 12, 25% yield from 5)], and the major product (12) was taken forward in the synthesis as a pure isomer. Its structure was confirmed by eventual conversion to epothilone A (1). The olefin metathesis reaction of 12 proceeded smoothly in the presence of $RuCl_2(=CHPh)(PCy_3)_2$ catalyst[14] in dilute $CH_2Cl_2$ solution at 25 °C to afford, in 50% yield, the *Z*-olefin 13,[15] together with its *E*-isomer (35%)[15]. After chromatographic purification [silical gel, benzene:ethyl acetate:hexane (2:1:2), $R_f$ = 0.21 (*Z*-isomer), 0.45 (*E*-isomer)], the silyl group was removed from macrocycle 13 by exposure to $CF_3COOH$ in $CH_2Cl_2$ at 0 °C to afford the dihydroxy lactone 14 in 98% yield. Finally, selective epoxidation of the $\Delta^{12,13}$-double bond of 14 was effected with *m*CPBA in $CH_2Cl_2$ at 0 °C to afford epothilone A (1) in 55% yield [silica gel, methanol:$CH_2Cl_2$ (1:20), $R_f$ = 0.23], together with its 12α,13α-epoxide isomer [20% yield, silica gel, methanol:$CH_2Cl_2$ (1:20), $R_f$ = 0.16] and its regioisomer 15 [20% yield, silica gel, methanol:$CH_2Cl_2$ (1:20), $R_f$ = 0.22, stereochemistry unassigned]. Chromatographically purified synthetic epothilone A (1) exhibited identical properties ($^1$H and $^{13}$C NMR, Mass spec, $[\alpha]_D$, TLC and HPLC) to those of an authentic natural sample.[16]

The reported total synthesis demonstrates the power of the olefin metathesis reaction in complex molecule construction and renders epothilone A (1) readily accessible. Most importantly, its brevity, convergent nature and flexibility should allow the generation of a diverse epothilone library for further biological investigations. In addition to the olefin metathesis approach reported herein, Figure 1 points to at least two more, distinctly different approaches to epothilones: (a) a macrolactonization approach; and (b) an approach in which an intramolecular aldol reaction may play the crucial role of constructing the macrocyclic skeleton. These and other strategies towards these compounds are currently under investigation in these laboratories.[17,18]

**References**


[1] a) G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-4138042, 1993 (*Chem. Abstr.* 1993, *120*, 52841); b) K. Gerth, N. Bedorf, G Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.*, 1996, *49*, 560-563.

[2] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* 1996, *108*, 1671-1673; *Angew Chem. Int. Ed. Engl.* 1996, *35*, 1567-1569.

[3] M.R. Grever, S.A. Schepartz, B.A. Chabner, *Seminars in Oncology* 1992, *19*, 622-638.

[4] D.M. Bollag, P.A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C.M. Woods, *Cancer Res.* 1995, *55*, 2325-2333.

[5] K.C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* 1994, *106*, 38-67; *Angew. Chem. Int. Ed. Engl.* 1994, *33*, 15-44.

[6] K.C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* 1996, *108*, 2554-2556; *Angew. Chem. Int. Ed. Engl.* 1996, *35*, 2399-2401. For other studies in the epothilone field, see: a) D. Meng, E.J. Sorensen, P. Bertinato, S.J. added Danishefsky, *J. Org. Chem.* 199[illegible] 98-7999. b) P. Bertinato, E.J. Sorensen, D. Meng, S.J. Danishefsky, *J. Org. Chem.* 1996, *61*, 8000-8001; c) D. Shinzer, A.

Limberg, O.M. Böhm, *Chem. Eur. J.* 1996, *2*, 1477-1482. For the first total synthesis of epothilone A, see: A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E.J. Sorensen, S.J. Danishefsky, *Angew. Chem.* 1996, *108*, 2976-2978, *Angew. Chem.* 1996, *35*, 2801-2803.

[7] For the development of the olefin metathesis as a ring forming reaction, see a) W. J. Zuercher, M. Hashimoto, R.H. Grubbs, *J. Am. Chem. Soc.* 1996, *118*, 6634-6640; b) P. Schwab, R.H. Grubbs, J.W. Ziller, *J. Am. Chem. Soc.* 1996, *118*, 100-110; c) R.H. Grubbs, S.J. Miller, G.C. Fu, *Acc. Chem. Res.* 1995, *28*, 446–452 and references cited therein. For some earlier pioneering studies on this reaction, see: a) T.J. Katz, S.J. Lee, N. Acton, *Tetrahedron Lett.* 1976, 4247–4250; b) T.J. Katz, N. Acton, *Tetrahedron Lett.* 1976, 4251–4254; c) T.J. Katz, J. McGinnis, C. Altus, *J. Am. Chem. Soc.* 1976, *98*, 606–608; d) T.J. Katz, *Advances in Organomet. Chem.* 1977, *16*, 283-317.

[8] Ketoaldehyde **11** was prepared from propionyl chloride according to a literature procedure: T. Inukai, R. Yoshizawa, *J. Org. Chem.* 1967, *32*, 404–407.

[9] U.S. Racherla, H.C. Brown, *J. Org. Chem.* 1991, *56*, 401–404

[10] Mosher ester analysis ($^1$H NMR) revealed >97% enantiomeric purity for compounds **3** and **10**.

[11] M.W. Bredenkamp, C.W. Holzapfel, W. J. van Zyl, *Synthetic Commun.* 1990, *20*, 2235-2249.

[12] A. Fürstner, K. Langemann, *J. Org. Chem.* 1996, *61*, 3942-3943.

[13] In this reaction (unoptimized) the 8-membered lactone corresponding to **11** was also observed (10-15%).

[14] P. Schwab, M.B. France, J.W. Ziller, R.H. Grubbs, *Angew. Chem.* 1995, *107*, 2179-2181; *Angew. Chem. Int. Ed. Engl.* 1995, *34*, 2039-2041.

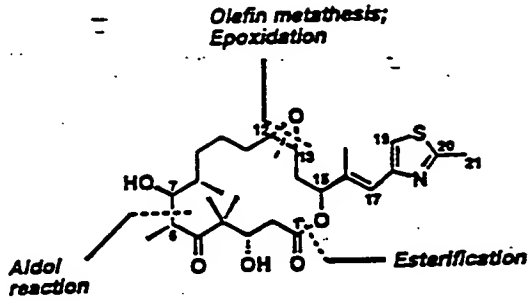
[15] Decoupling experiments ($^1$H NMR, 500 MHz, $CDCl_3$) revealed coupling constants (*J*) for $H_{12}/H_{13}$ of 11.0 Hz for the Z-isomer (**13**) and 15.0 Hz for the *E*-isomer.

[16] We thank Dr. G. Höfle for kindly providing us with a natural sample of epothilone A (1).

[17] Selected physical properties of compounds: 12: $R_f$ = 0.29 [silica gel, ethyl acetate:hexane (1:5)]; $[\alpha]_D$ = -53.4 (c = 1.0, MeOH); IR (film): 3508 (br, OH), 1736 (C(O)O), 1690 (COC), 1650 $cm^{-1}$(CH=CHCO); $^1$H-NMR (500 MHz, $CDCl_3$): δ = 6.93 (s, 1 H, -C=CH-S-), 6.47 (s, 1 H, -C=CH-C=), 5.81-5.72 (m, 1 H, -C*H*=$CH_2$), 5.73-5.65 (m, 1 H, -C*H*-$CH_2$), 5.27 (dd, 1 H, $J_1$= 7.0 Hz, $J_2$= 6.5 Hz, -O-CH-), 5.06 (dd, 2 H, $J_1$ = 17.5 Hz, $J_2$ = 10.0 Hz, -CH=C$H_2$), 4.92 (dd, 2 H, $J_1$ = 17.0 Hz, $J_2$ = 10.5 Hz, -CH=C$H_2$), 4.39 (dd, 1 H, $J_1$ = 4.0 Hz, $J_2$ = 6.0 Hz, -$(CH_3)_2$C-C*H*-), 3.42 (bs, 1 H, -OH), 3.28 (q, 1 H, $J$ = 7.0 Hz, -C*H*($CH_3$)C(O)-), 3.24 (d, 1 H, $J$ = 9.5 Hz, -C*H*(OH)), 2.67 (s, 3 H, -S-C($CH_3$)=N-), 2.54-2.43 (m, 2 H), 2.43 (dd, 1 H, $J_1$ = 4.0 Hz, $J_2$= 10.0 Hz, -C$H_2$-COO-), 2.31 (dd, 1 H, $J_1$= 6.0 Hz, $J_2$= 10.0 Hz, -C$H_2$-COO-), 2.04 (s, 3 H, -C($CH_3$)=C-), 1.95 (m, 2 H, -C$H_2$-CH=$CH_2$), 1.75-1.65 (m, 1 H), 1.48-1.43 (m, 1 H), 1.43-1.36 (m, 1 H), 1.22-1.10 (m, 2 H), 1,17 (s, 3 H, -C$(CH_3)_2$-), 1,09 (s, 3 H, -C$(CH_3)_2$-), 1.01 (d, 3 H, $J$ = 6.5 Hz, -C(O)-CH($CH_3$)-), 0.86 (s, 9 H, -SiC$(CH_3)_3(CH_3)_2$), 0.81 (d, 3 H, $J$ = 7.0 Hz, -C(OH)-CH($CH_3$)-), 0.09 (s, 3 H, -SiC$(CH_3)_3(CH_3)_2$), 0.04 (s, 3 H, -SiC$(CH_3)_3(CH_3)_2$); $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 221.8, 170.9, 164.6, 152.4, 139.0, 136.6, 133.2, 121.0, 117.8, 116.4, 114.1, 78.8, 74.5, 73.4, 53.9, 41.2, 40.1, 37.4, 35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.9, 19.2, 18.1, 15.2, 14.6, 9.7, -4.3, -4.9; HRMS calcd for $C_{34}H_{57}NO_5SSi$ ($M+Cs^+$): 752.2781, found: 752.2760. 13: $R_f$ = 0.21 [silica gel, ethyl acetate : benzene : hexanes (1:2:2)]; $[\alpha]_D$ = -97 (c = 0.2, MeOH); IR (film): 3456 (br, OH), 1739 (C(O)O), 1692 (COC); $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.94 (s, 1 H, -C=CH-S-), 6.56 (s, 1 H, -C=CH-C=), 5.45 (dd, 1 H, $J_1$ = 10.5 Hz, $J_2$ = 3.0 Hz, -CH=C*H*-$CH_2$-), 5.35 (m, 1 H, -C*H*=CH-$CH_2$-), 5.02 (d, 1 H, $J$ =10.0 Hz, -O-CH-), 4.06 (dd, 1 H, $J_1$ =7.0 Hz, $J_2$ =5.5 Hz, -$C(CH_3)_2$-C*H*-), 3.94 (bt, 1 H, -C*H*(OH)-), 3.05 (dq, 1 H, $J_1$ =3.0 Hz, $J_2$ =6.5 Hz, -C(O)-C*H*($CH_3$)-), 3.00 (bs, 1 H, -OH), 2.82-2.78 (m, 2 H),

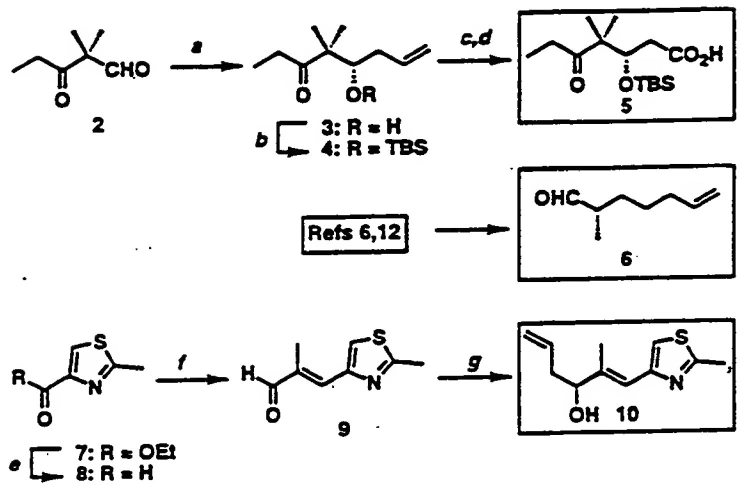
2.78-2.69 (m, 1H), 2.71 (s, 3 H, -S-C($CH_3$)=N-), 2.40-2.30 (m, 1 H), 2.10 (s, 3 H, -C($CH_3$)=CH-C=), 2.10-2.00 (m, 1 H), 1.99-1.90 (m, 1 H), 1.75-1.65 (m, 1 H), 1.7-1.50 (m, 2 H), 1.45-1.35 (m, 1 H), 1.21 (m, 1 H, -CH($CH_3$)-$CH_2$-$CH_2$-), 1.17 (s, 6 H, -C($CH_3$)$_2$-), 1.14 (d, 3 H, $J$ = 5.0 Hz, -C(O)-CH($CH_3$)-), 1.02 (d, 3 H, $J$ =5.0 Hz, -CH($CH_3$)-), 0.82 (s, 9 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.12 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.05 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$); $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 218.1, 170.9, 164.7, 138.2, 134.7, 124.0, 119.6, 119.4, 116.0, 79.0, 76.3, 73.2, 53.5, 43.0, 39.1, 38.8, 33.6, 31.9, 28.4, 27.8, 26.1, 24.8, 22.9, 19.2, 18.6, 16.5, 15.3, 14.1, -3.6, -5.5; HRMS calcd for $C_{32}H_{53}NO_5SSi$ ($M$ +$Cs^+$): 724.2468, found: 724.2479. 1: $R_f$ = 0.23 [silica gel, MeOH : $CH_2Cl_2$ (1:2)]; HPLC [Watman EOC, C-18, 4 μ, 108 x 4.6 mm column, solvent: gradient: 0→20 min, 30→80 % MeOH in $H_2O$, $R_t$ = 14.8 min; $[\alpha]_D$ = -45.0 (c = 0.02, MeOH); $^1$H NMR (500 MHz, $C_6D_6$): δ = 6.78 (s, 1 H, -C=CH-S-), 6.52 (s, 1 H, -C=CH-C=), 5.52 (dd, 1 H, $J_1$ = 6.0 Hz, $J_2$ = 2.0 Hz, -O-CH), 4.24 (d, 1 H, $J$ =10.0 Hz, -CH(OH)-), 3.86 (m, 1 H,-$CH$(OH)), 3.81 (bs, 1 H, -OH), 3.10 (m, 1 H, -$CH_2$-$CHO$-), 2.84 (m, 1 H, -C(O)-CH-), 2.67 (m, 1 H, -$CH_2$-$CHO$-), 2.49 (dd, 1 H, $J_1$ = 11.0 Hz, $J_2$ =14.5 Hz, -OOC-$CH_2$-), 2.27 (s, 3 H, -S-C($CH_3$)=N-), 2.24 (dd, 1 H, $J_1$ = 14.5 Hz, $J_2$ = 3.5 Hz, OOC-$CH_2$-), 2.11 (s, 3 H, -C($CH_3$)=), 1.92 (m, 1 H, -$CH_2$-CHO-), 1.84 (m, 1 H, -$CH_2$-CHO-), 1.74 (m, 1 H), 1.57 (m, 1 H), 1.27-1.42 (m, 5 H), 1.11 (d, 3 H, $J$ = 7.0 Hz, -C(O)-CH($CH_3$)-), 1.09 (s, 3 H, -C($CH_3$)$_2$-), 1.03 (s, 3H, -C($CH_3$)$_2$-), 1.01 (s, 3H, -CH($CH_3$)-); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 218.7, 169.9, 164.1, 152.6, 137.2, 119.5, 119.3, 76.3, 74.8, 73.1, 56.9, 53.9, 52.6, 43.4, 38.8, 36.0, 31.4, 30.0, 27.0, 23.6, 20.8, 20.2, 18.4, 17.0, 15.4, 14.3; HRMS calcd for $C_{26}H_{39}NO_6S$ ($M$ +$Cs^+$): 626.1552, found: 626.1551.

[18] All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Second sentence was deleted.

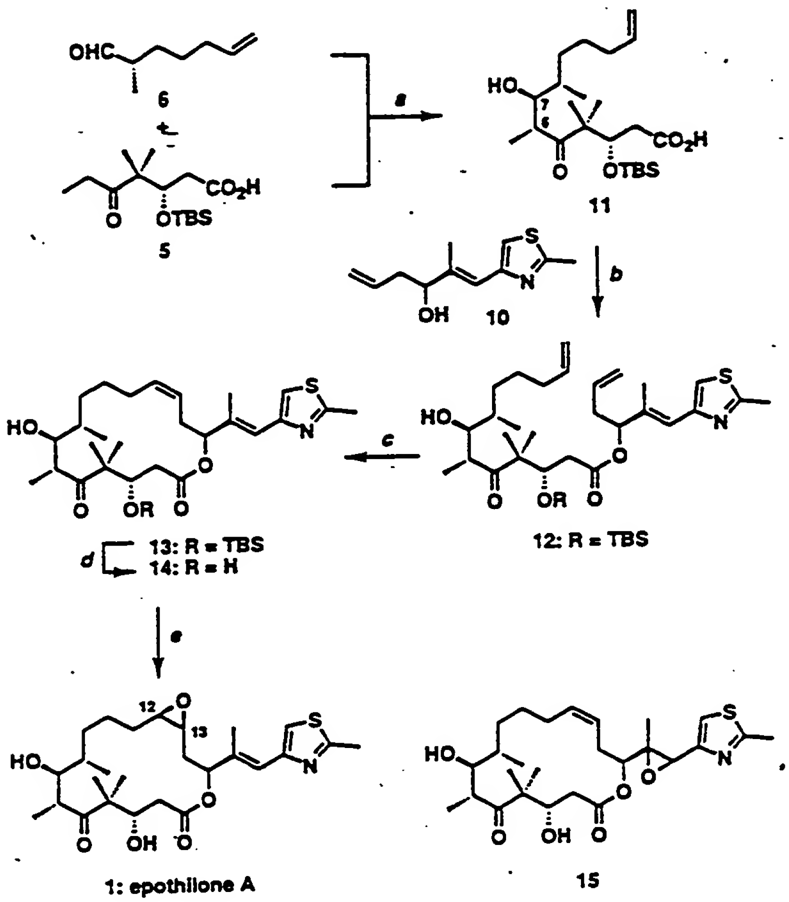



1: epothilone A

**Figure 1. Structure and retrosynthetic analysis of epothilone A (1).**



Scheme 1. Synthesis of building blocks 5, 6 and 10. a. 1.1 equiv. of (+)-Ipc$_2$B(allyl), Et$_2$O, -100 °C, 0.5 h, 74%; b. 1.1 equiv. of TBSOTf, 1.2 equiv. of 2,6-lutidine, $CH_2Cl_2$, 25 °C, 1 h, 98%; c. $O_3$, $CH_2Cl_2$, -78 °C, 0.5 h; then excess $Ph_3P$, -78 to 25 °C, 1 h, 82%; d. 3 equiv. of $NaClO_2$, 4 equiv. of 2-methyl-2-butene, 1.5 equiv. of $NaH_2PO_4$, $^t$BuOH:$H_2O$ (5:1), 25 °C, 2 h, 93%. e. 1.1 equiv. of Dibal-H, $CH_2Cl_2$, -78 °C, 0.5 h, 90%; f. 1.1 equiv. of $Ph_3P$=C(Me)CHO, benzene, 80 °C, 1 h, 90%; g. 1.1 equiv. of (+)-Ipc$_2$B(allyl), Et$_2$O, -100 °C, 0.5 h, 96%. TBS = *tert*-butyldimethylsilyl; Ipc$_2$B(allyl) = diisopinocampheylallyl borane.




Scheme 2. Synthesis of epothilone A (1): a. 2.2 equiv. of LDA, THF, -78 to -40 °C, 0.5 h; then 1.2 equiv. of 6 in THF, -78 to -40 °C, 0.5 h, high yield of 11 and its 6*S*,7*R*-diastereomer; b. 2.0 equiv. of 10, 1.5 equiv. of DCC, 1.5 equiv. of 4-DMAP, toluene, 25 °C, 12 h, 12 (45% overall yield from 5), plus 6*S*,7*R*-diastereomer of 12 (25% overall yield from 5); c. 12 (0.006 M in $CH_2Cl_2$), 15 mol % of $RuCl_2(=CHPh)(PCy_3)_2$ cat., 25 °C, 8 h, 50%, plus $\Delta^{12,13}$-*trans* isomer of 13 (35%); d. $CF_3COOH$ (20% by volume), $CH_2Cl_2$, 0 °C, 4 h, 98%; e. 1.1 equiv. of *m*CPBA, benzene, 0 °C, 20 h, 1 (55%), plus 12α,13α-epoxide (20%), plus regioisomeric epoxide 15 (20%). LDA = lithium diisopropylamide, DCC = dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylaminopyridine.

REVISED

# Total Synthesis of Epothilone A: The Macrolactonization Approach[**,†]

[†] This paper is dedicated to Professor Stephen Hanessian on the occasion of his 60th birthday.

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**Keywords:** epothilone, total synthesis, macrolactonization

**Table of Content Text**

A highly convergent and practical total synthesis of the antitumor agent epothilone A based on a macrolactonization strategy has been developed. The route may lead to a diverse library of epothilones for biological screening.

Scheme


epothilone A

The novel molecular structures of the epothilones (e.g. epothilone A, 1, Figure 1) coupled with their antifungal[1,2] and antitumor activities[1-4] and microtubule binding properties[4] promise an exciting new chapter in chemistry, biology and medicine. Particularly intriguing is the ability of these compounds to displace taxol from its binding site on microtubules,[4] towards which they exhibit much higher affinity[4] than taxol.[5] An indication of the intense interest in this field is the flurry of activities[6] directed toward their total synthesis within the relatively short time since their structural elucidation.[2] While our first total synthesis[6f] of epothilone A (**1**) enjoys the benefits of the olefin metathesis reaction, the one we wish to report here relies on a macrolactonization process to construct the main ring skeleton of this target molecule. In addition, the reported synthesis is highly convergent and flexible so as to allow entry into a large library of epothilones, including epothilone B and all of the $2^6$ stereoisomers of epothilone A (**1**).

Figure 1 outlines, in retrosynthetic terms, the macrolactonization approach to epothilone A (**1**). This analysis leads to a convergent strategy by which three fragments ($C_1$-$C_6$, $C_7$-$C_{12}$ and $C_{13}$-$C_{21}$), each containing a stereogenic center, are to be constructed stereoselectively via asymmetric synthesis procedures followed by their union and elaboration to the final target. For the coupling of these fragments, a Wittig reaction and an aldol reaction will be utilized, whereas the C(O)-O bond formation is reserved as the macrocycle forming process in the form of a macrolactonization. It is important to note that the designed strategy allows for the preparation of all possible stereisomers of epothilone A (**1**) since the configuration of each stereocenter can easily be reversed.

The execution of this rather simple strategy towards epothilone A (**1**) proceeded smoothly as summarized in Scheme 1. Thus, the SAMP derivative **2**, obtained by reaction of SAMP[7] with propionaldehyde, was alkylated with 4-iodo-1-benzyloxybutane in the presence of LDA in THF at -100 °C according to the method of Enders[7] t

produce compound **3** in 92% yield and >98% e.e.[8] Ozonolysis of **3** followed by treatment with $NaBH_4$ furnished alcohol **5**, via aldehyde **4**, in 77% overall yield. Protection of the hydroxyl group in **5** as a *tert*-butyldimethylsilyl (TBS) ether followed by standard elaboration of the other end of the molecule (hydrogenolysis of benzyl ether; iodonation; and phosphonium salt formation) then yielded the desired fragment **9** in 55% overall yield (from **5**).

The second requisite fragment, thiazoline aldehyde **13**, was rapidly constructed from the thiazoline derivative **10**[6f] by (a): silylation (TBSCl, imidazole, 99%); (b): selective 1,2-dihydroxylation[9] (AD-mix-β, 79%); and (c): $Pb(OAc)_4$ cleavage (99%). Generation of the phosphorane **14** from phosphonium salt **9** with sodium hexamethydisilylamide (NaHMDS), followed by addition of aldehyde **13** led, predominently, to the *Z*-olefin **15** in 69% yield (*Z*:*E* *ca* 9:1). The primary TBS group was selectively removed from **15** with camphorsulfonic acid (CSA) in MeOH to give alcohol **16** (86% yield) which was oxidized to the corresponding aldehyde (**17**) by the action of $SO_3$.*pyr*. (82% yield). Condensation of the dilithioderivative of **18**[6f] (2.6 equiv. of LDA, THF, -78 to -40 °C) with aldehyde **17** proceeded at -78 °C to afford a mixture of diastereomers (**19** + 6*S*,7*R*-diastereomer; *ca* 1:1 to 1:2 ratio, depending on precise conditions) in good yield. This mixture was carried through the sequence until compound **21**, at which stage it was separated by silica gel chromatography into its components. Thus, the aldol products (**19** + diastereomer) were fully silylated with TBSOTf/ 2,6-lutidine, and the resulting mixture of *tetra*-TBS derivatives (compound **20** + diastereomer) was briefly exposed to $K_2CO_3$ in MeOH to afford, after preparative TLC, pure carboxylic acid **21** (31% overall yield), and its 6*S*,7*R*-diastereomer (30% overall yield from **17**) (**21**: *Rf* = 0.61, 6*S*,7*R*-diastereomer: *Rf* = 0.70, silica gel, 5% MeOH in $CH_2Cl_2$). The indicated stereochemical assigment for the slower moving isomer **21** was based on its succesfull conversion to macrolactone **24**[6f] and epothilone A (**1**).

At this stage, it was necessary to selectively deprotect the C-15 hydroxyl group for the purposes of the intended macrolactonization reaction. This task was succesfully accomplished with *tetra-n*-butylammonium fluoride (TBAF) in THF at 25 °C, leading to the desired hydroxy acid **22** in 78% yield. Steric hindrance at the sites of the other TBS groups was presumed to be responsible for this selectivity. The key ring closure of **22** was smoothly effected under Yamaguchi conditions[10] (2,4,6-trichlorobenzoyl chloride, $Et_3N$, 4-DMAP, THF-toluene, 25 °C) furnishing the 16-membered ring lactone **23** in 90% yield. Finally, exposure of **23** to $CF_3COOH$ (20% by volume) in $CH_2Cl_2$ at 0 °C led to the targeted olefinic diol **24** (92% yield). The latter compound was then converted to epothilone A (**1**) by exposure to *m*CPBA as already described.[6f]

This expedient route to epothilone A (**1**) may easily be extended to epothilone B and to a variety of analogs of these naturally occurring compounds for biological investigations. Indeed, the molecular design, chemical synthesis and biological screening of such analogs should be among the next priorities in this field.[11]

Table 1. Selected physical properties of compounds **21**, **22** and **23**.

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**21**: $R_f$ = 0.61 [silica gel, methanol:dichloromethane (5%)]; $[\alpha]^{22}_D$ = -8.8 ($c$ = 0.8 in chloroform); IR (film): 2931, 2856, 1712, 1466, 1254, 1083, 836 $cm^{-1}$; $^1$H-NMR (600 MHz, $CDCl_3$): $\delta$ = 6.94 (s, 1 H, -C=CH-S-), 6.61 (s, 1 H, -C=CH-C=), 5.44-5.41 (m, 2 H, -CH=C*H*-$CH_2$-, -C*H*=CH-$CH_2$-), 4.40 (dd, 1 H, $J_1$ = 3.2 Hz, $J_2$ = 6.5 Hz, -$(CH_3)_2$C -C*H*-), 4.11 (dd, 1 H, $J_1$ = 5.9 Hz, $J_2$ = 6.5 Hz, -C*H*(OSi$(CH_3)_2$*t*-Bu)-), 3.75 (dd, 1 H, $J_1$ = 3.0 Hz, $J_2$ = 6.5 Hz, TBSO-C*H*-CH(Me)), 3.12 (dq, 1 H, $J_1$ = 7.0 Hz, $J_2$ = 6.5 Hz, -C(O)-C*H*($CH_3$)-), 2.69 (s, 3 H, -S-C($CH_3$)=N-), 2.48 (dd, 1 H, $J_1$ = 3.2 Hz, $J_2$ = 16.0 Hz, -C$H_2$-COOH), 2.35 (dd, 1 H, $J$ = 6.7 Hz, $J$ = 16.0 Hz, -C$H_2$-COOH), 2.31-2.28 (m, 2 H, -C$H_2$-CH=CH), 2.10-2.00 (m, 2 H, -C$H_2$-CH=CH), 1.95 (s, 3 H, -C(C$H_3$)=CH-C=), 1.42-1.30 (m, 5 [illegible] 1.18 (s, 3 H, -C(C$H_3$)$_2$-), 1.10 (s, 3 H, -C(C$H_3$)$_2$-), 1.06 (d, 3 H, $J$ = 7.0 Hz, -

C(O)-CH($CH_3$)-), 0.90-0.85 (m, 30 H, -C(O)-CH($CH_3$)-, 3 x -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.12 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.09 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.07 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.05 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.04 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.03 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$); $^{13}$C-NMR (600 MHz, $CDCl_3$): δ: 218.2, 176.1, 164.9, 152.7, 142.8, 131.4, 126.0, 118.5, 114.7, 78.7, 73.3, 53.7, 44.7, 40.0, 39.0, 34.7, 30.8, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.0, 18.8, 18.5, 18.2, 17.2, 15.8, 13.8, -3.8, -3.9, -4.2, -4.6, -4.7, -4.9; HRMS calcd for $C_{44}H_{83}NO_6SSi_3$ ($M + Cs^+$); 970.4303, found: 970.4318.

**22**: $R_f$ = 0.40 [silica gel, methanol:dichloromethane (5%)]; $[\alpha]^{22}_D$ = -19.2 ($c$ = 0.1 in chloroform); IR (film): 3358 (br, OH), 2932, 2857, 1701, 1466, 1254, 1088, 988, 835; $^1$H NMR (600 MHz, $CDCl_3$): δ = 6.95 (s, 1 H, -C=CH-S-), 6.61 (s, 1 H, -C=CH-C=), 5.58-5.54 (m, 1 H, -CH=$CH$-$CH_2$-), 5.43-5.39 (m, 1 H, -$CH$=CH-$CH_2$-), 4.39 (dd, 1H, $J_1$ = 3.9 Hz, $J_2$ = 6.7 Hz, -($CH_3$)$_2$C -$CH$-), 4.18 (dd, 1 H, $J_1$ = 5.0 Hz, $J_2$ = 7.5 Hz, -$CH$(OH)-), 3.78 (dd, 1 H, $J_1$ = 3.0 Hz, $J_2$ = 6.9 Hz, -SiO-$CH$-CH(Me)), 3.11 (dq, 1 H, $J_1$ = 6.9 Hz, $J_2$ = 6.7 Hz, -C(O)-$CH$($CH_3$)-), 2.70 (s, 3 H, -S-C($CH_3$)=N-), 2.43 (dd, 1 H, $J_1$ = 3.9 Hz, $J_2$ = 16.2 Hz, -$CH_2$-COOH), 2.40-2.35 (m, 2 H, -$CH_2$-CH=), 2.35 (dd, 1 H, $J_1$ = 6.7 Hz, $J_2$ = 16.2 Hz, -$CH_2$-COOH), 2.15-2.10 (m, 1 H, -$CH_2$-CH=), 2.00 (s, 3 H, -C($CH_3$)=CH-C=), 1.99-1.95 (m, 1 H, -$CH_2$-CH=), 1.48-1.30 (m, 5 H), 1.18 (s, 3 H, -C($CH_3$)$_2$-), 1.08 (s, 3 H, -C($CH_3$)$_2$-), 1.05 (d, 3 H, $J$ = 6.7 Hz, -C(O)-CH($CH_3$)-), 0.89-0.84 (m, 21 H, -C(O)-CH($CH_3$)-, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.09 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.05 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.04 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.03 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$); $^{13}$C-NMR (600 MHz, $CDCl_3$): δ: 218.9, 175.4, 166.3, 152.8, 134.4, 125.7, 119.5, 115.9, 74.4, 74.3, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8, 27.0, 26.9, 24.4, 22.0, 21.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, 8.6, -2.9, -3.1, -3.3, -3.8; HRMS calcd for $C_{38}H_{69}NO_6SSi_2$ ($M + Cs^+$); 856.3439, found: 856.3459.

**23**: $R_f$ = 0.37 [silica gel, hexane : ether (2:1); $[\alpha]^{22}_D$ = -22.9 ($c$ = 0.3 in chloroform); IR (film): 2926, 2854, 1734, 1693, 1463, 1381, 1252, 1099, 829; $^1$H-NMR (500 MHz, $CDCl_3$): δ = 6.98 (s, 1 H, -C=CH-S-), 6.58 (s, 1 H, -C=CH-C=), 5.53 (m, 1 H, -CH=$CH$-

$CH_2$-), 5.43-5.34 (m, 1 H, -C*H*=CH-$CH_2$-), 5.00 (d, 1 H, $J$ = 6.0 Hz, -O-CH), 4.03 (d, 1 H, $J$ = 10.0 Hz, -CH(OH)-), 3.89 (d, 1 H, $J$ = 9.0 Hz, -C*H*(OH)), 3.04-2.98 (m, 1 H, -C(O)-C*H*-), 2.85 (d, 1 H, $J$ = 15.0 Hz, OOC-$CH_2$-), 2.72 (s, 3 H, -S-C($CH_3$)=N-), 2.66 (dd, 1 H, $J_1$ = 15.0 Hz, $J_2$ = 10.0 Hz, OOC-$CH_2$-), 2.42-2.31 (m, 2 H), 2.11 (s, 3 H, -C($CH_3$)=), 1.92-1.83 (m, 1 H), 1.66-1.38 (m, 4 H), 1.20 (s, 3 H, -C($CH_3$)$_2$-), 1.16 (s, 3 H, -C($CH_3$)$_2$, 1.09 (d, 3 H, $J$ = 7.0 Hz, -C(O)-CH($CH_3$)-), 0.95 (d, 3 H, $J$ = 7.0 Hz, -CH($CH_3$)-), 0.94 (s, 9 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.85 (s, 9 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.12 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.10 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), 0.08 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$), -0.10 (s, 3 H, -SiC($CH_3$)$_3$($CH_3$)$_2$). $^{13}$C-NMR (600 MHz, $C_6D_6$): δ: 215.0, 171.3, 135.1, 122.7, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.0, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, -3.1, -3.2, -3.7, -5.8; HRMS calcd for $C_{38}H_{67}NO_5SSi_2$ ($M + H^+$); 706.4357, found: 706.4382.

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## References


[1] a) G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-4138042, **1993** (*Chem. Abstr.* **1993**, *120*, 52841); b) K. Geth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 560-563.

[2] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671-1673; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567-1569.

[3] M. R. Grever, S. A. Schepartz, B. A. Chabner, *Seminars in Oncology* **1992**, *19*, 622-638.

[4] D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, *55*, 2325-2333.

[5] K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38-67; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44.

[6] a) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554-2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399-2401; b) D. Meng, E. J. Sorensen, P. Bertinato, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 7998-7999; c) P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 8000-8001; d) D. Schinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J.* **1996**, *2*, 1477-1482. For the first total synthesis of epothilone A (**1**), see: e) A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2801-2803; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2976-2978. For an olefin metathesis based total synthesis of epothilone A (**1**), see: f) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 0000; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 0000.

[7] a) D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *112*, 2933-2960; b) D. Enders, J. Tiebes, N. De Kimpe, M. Keppens, C. Stevens, G. Smagghe, O. Betz, *J. Org. Chem.* **1993**, *58*, 4881-4884; c) D. Enders, A. Plant, D. Backhaus, U. Reinhold, *Tetrahedron* **1995**, *51*, 10699-10714; d) D. Enders, *Asymmetric Synthesis* **1984**, *Vol 3*, 275-339, Academic Press, Inc. We thank Prof. Enders for a generous gift of SAMP.

[8] Only one diastereomer is detected in the 500 MHz $^1H$ NMR spectrum ($CDCl_3$) of compound **3**.

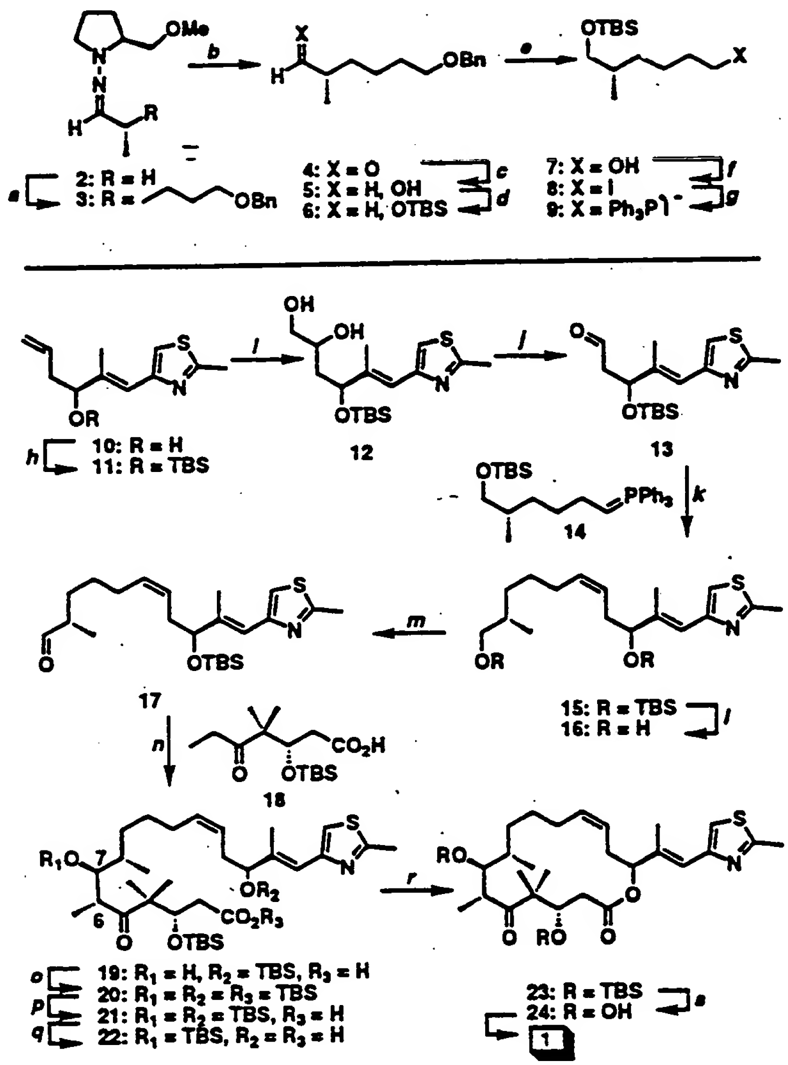
[9] a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem Rev.* **1994**, *94*, 2483-2547; b) T. Sammakia, T. B. Hurley, D. M. Sammond, R. S. Smith, *Tetrahedron Lett.* **1996**, *37*, 4427-4430.

[10] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; b) J. Mulzer, P. A. Mareski, J. Buschmann, P. Luger, *Synthesis* **1992**, 215-228; c) K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter,

H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski: *Chem. Eur. J.* **1996**, *2*, 847-868.

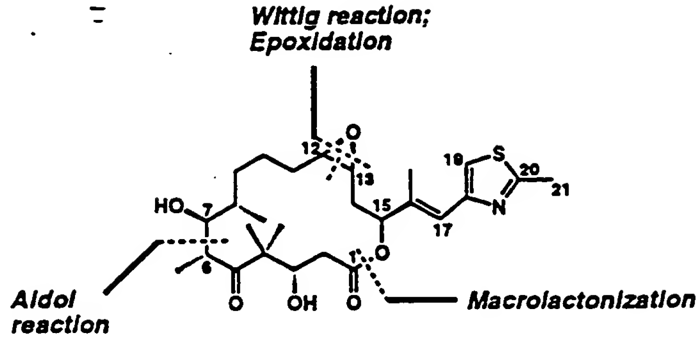
[11] All new compounds exhibited satisfactory spectral and analytical and/or exact mass data.

Scheme 1. Total synthesis of epothilone A (1): a. 1.1 equiv. of LDA, THF, 0 °C, 8 h; then 1.5 equiv. of 4-iodo-1-benzyloxybutane in THF, at –100 to 0 °C, 6 h, 92%; b. $O_3$, $CH_2Cl_2$, –78 °C, 77%; c. 3.0 equiv. of $NaBH_4$, MeOH, 0 °C, 15 min, 98 %; d. 1.5 equiv. of TBSCl, 2.0 equiv. of $Et_3N$, $CH_2Cl_2$, 0 °C to 25 °C, 12 h, 95%; e. $H_2$, $Pd(OH)_2$ cat., THF, 3 h, 25 °C, 70%; f. 1.5 equiv. of $I_2$, 3.0 equiv. of imidazole, 1.5 equiv. of $Ph_3P$, $Et_2O/CH_3CN$ [3 : 1], 0 °C, 0.5 h, 91%; g. $Ph_3P$, neat, 100 °C, 2 h, 86%; h. 1.5 equiv. of TBSCl, 2.0 equiv. of imidazole, THF, 0 to 25 °C, 1 h, 99%; i. 2.4 g/mmol of AD-mix-β, *t*-BuOH/$H_2O$ [1 : 1], 25 °C, 8 h, 79%; j. 1.1 equiv. of $Pb(OAc)_4$, EtOAc, 0°C, 10 min, 99%; k. 1.2 equiv. of 9, 1. 2 equiv. of NaHMDS, THF, 0 °C, 0.25 h, then add 1.0 equiv. of aldehyde 13, 0 °C, 15 min, 69% (*Z* : *E* *ca.* 9 : 1); l. 1.0 equiv. of CSA portionwise over 1 h, $CH_2Cl_2$/MeOH [1 : 1], 0 °C, then 25 °C, 0.5 h, 86%; m. 2.0 equiv. of $SO_3$.*pyr.*, 10.0 equiv. of DMSO, 5.0 equiv. of $Et_3N$, $CH_2Cl_2$, 25 °C, 0.5 h, 82%; n. 3.0 equiv. of LDA, THF, 0 °C, 0.25 h; then 1.2 equiv. of 18 in THF, –78 to –40 °C, 0.5 h, then 1.0 equiv. of 17 in THF at –78 °C, high yield of 19 and its 6*S*,7*R*-diasteromer (*ca.* 1 : 1 ratio); o. 3.0 equiv. of TBSOTf, 5.0 equiv. of 2,6-lutidine, $CH_2Cl_2$, 0 °C, 2 h; p. 2.0 equiv. of $K_2CO_3$, MeOH, 25 °C, 15 min, 31% of 21 and 30% of its 6*S*,7*R*-diasteromer from 17; q. 6.0 equiv. of TBAF, THF, 25 °C, 8 h, 78%; r. 5 equiv. of 2,4,6-trichlorobenzoylchloride, 6.0 equiv. of $Et_3N$, THF, 25 °C, 15 min, then add to a solution of 10.0 equiv. of 4-DMAP in toluene (0.002 M based on 22), 25 °C, 0.5 h, 90%; s. 20% $CF_3COOH$ [by volume] in $CH_2Cl_2$, 0 °C, 1 h, 92%. LDA = lithium diisopropylamide; 4-DMAP = 4-dimethylaminopyridine; TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium hexamethyldisilylamide; DMSO = dimethylsulfoxide; Tf = triflate.



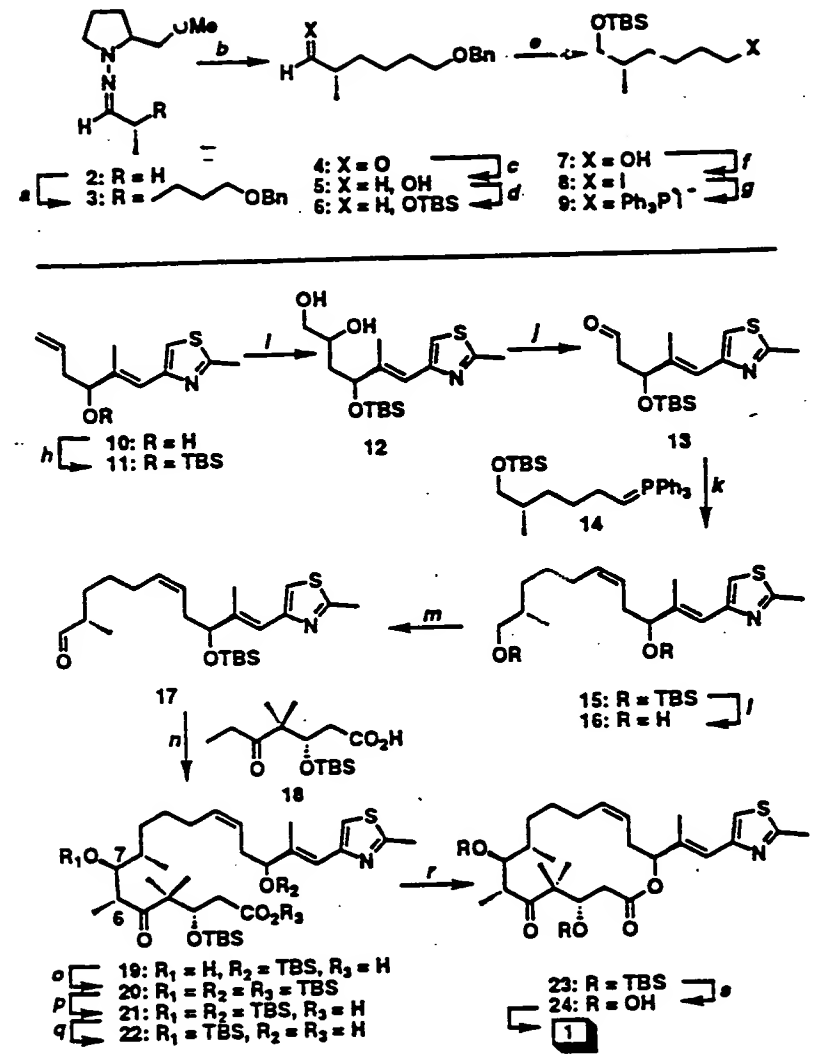
Scheme 1

Scheme 1. Total synthesis of epothilone A (1): a. 1.1 equiv. of LDA, THF, 0 °C, 8 h; then 1.5 equiv. of 4-iodo-1-benzyloxybutane in THF, at –100 to 0 °C, 6 h, 92%; b. $O_3$, $CH_2Cl_2$, –78 °C, 77%; c. 3.0 equiv. of $NaBH_4$, MeOH, 0 °C, 15 min, 98 %; d. 1.5 equiv. of TBSCl, 2.0 equiv. of $Et_3N$, $CH_2Cl_2$, 0 °C to 25 °C, 12 h, 95%; e. $H_2$, $Pd(OH)_2$ cat., THF, 3 h, 25 °C, 70%; f. 1.5 equiv. of $I_2$, 3.0 equiv. of imidazole, 1.5 equiv. of $Ph_3P$, $Et_2O/CH_3CN$ [3 : 1], 0 °C, 0.5 h, 91%; g. $Ph_3P$, neat, 100 °C, 2 h, 86%; h. 1.5 equiv. of TBSCl, 2.0 equiv. of imidazole, THF, 0 to 25 °C, 1 h, 99%; i. 2.4 g/mmol of AD-mix-β, *t*-BuOH/$H_2O$ [1 : 1], 25 °C, 8 h, 79%; j. 1.1 equiv. of $Pb(OAc)_4$, EtOAc, 0°C, 10 min, 99%; k. 1.2 equiv. of 9, 1. 2 equiv. of NaHMDS, THF, 0 °C, 0.25 h, then add 1.0 equiv. of aldehyde 13, 0 °C, 15 min, 69% (*Z* : *E ca.* 9 : 1); l. 1.0 equiv. of CSA portionwise over 1 h, $CH_2Cl_2$/MeOH [1 : 1], 0 °C, then 25 °C, 0.5 h, 86%; m. 2.0 equiv. of $SO_3$.*pyr.*, 10.0 equiv. of DMSO, 5.0 equiv. of $Et_3N$, $CH_2Cl_2$, 25 °C, 0.5 h, 82%; n. 3.0 equiv. of LDA, THF, 0 °C, 0.25 h; then 1.2 equiv. of 18 in THF, –78 to –40 °C, 0.5 h, then 1.0 equiv. of 17 in THF at –78 °C, high yield of 19 and its 6*S*,7*R*-diasteromer (*ca.* 1 : 1 ratio); o. 3.0 equiv. of TBSOTf, 5.0 equiv. of 2,6-lutidine, $CH_2Cl_2$, 0 °C, 2 h; p. 2.0 equiv. of $K_2CO_3$, MeOH, 25 °C, 15 min, 31% of 21 and 30% of its 6*S*,7*R*-diasteromer from 17; q. 6.0 equiv. of TBAF, THF, 25 °C, 8 h, 78%; r. 5 equiv. of 2,4,6-trichlorobenzoylchloride, 6.0 equiv. of $Et_3N$, THF, 25 °C, 15 min, then add to a solution of 10.0 equiv. of 4-DMAP in toluene (0.002 M based on 22), 25 °C, 0.5 h, 90%; s. 20% $CF_3COOH$ [by volume] in $CH_2Cl_2$, 0 °C, 1 h, 92%. LDA = lithium diisopropylamide; 4-DMAP = 4-dimethylaminopyridine; TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium hexamethyldisilylamide; DMSO = dimethylsulfoxide; Tf = triflate.




1: epothilone A

Figure 1. Structure and retrosynthetic analysis of epothilone A (1).



Scheme 1. Total synthesis of epothilone A (1): a. 1.1 equiv. of LDA, THF, 0 °C, 8 h; then 1.5 equiv. of 4-iodo-1-benzyloxybutane in THF, at −100 to 0 °C, 6 h, 92%; b. $O_3$, $CH_2Cl_2$, −78 °C, 77%; c. 3.0 equiv. of $NaBH_4$, MeOH, 0 °C, 15 min, 98 %; d. 1.5 equiv. of TBSCl, 2.0 equiv. of $Et_3N$, $CH_2Cl_2$, 0 °C to 25 °C, 12 h, 95%; e. $H_2$, $Pd(OH)_2$ cat., THF, 3 h, 25 °C, 70%; f. 1.5 equiv. of $I_2$, 3.0 equiv. of imidazole, 1.5 equiv. of $Ph_3P$, $Et_2O/CH_3CN$ [3 : 1], 0 °C, 0.5 h, 91%; g. $Ph_3P$, neat, 100 °C, 2 h, 86%; h. 1.5 equiv. of TBSCl, 2.0 equiv. of imidazole, THF, 0 to 25 °C, 1 h, 99%; i. 2.4 g/mmol of AD-mix-β, $^tBuOH/H_2O$ [1 : 1], 25 °C, 8 h, 79%; j. 1.1 equiv. of $Pb(OAc)_4$, EtOAc, 0°C, 10 min, 99%; k. 1.2 equiv. of 9, 1. 2 equiv. of NaHMDS, THF, 0 °C, 0.25 h, then add 1.0 equiv. of aldehyde 13, 0 °C, 15 min, 69% (*Z* : *E* *ca.* 9 : 1); l. 1.0 equiv. of CSA portionwise over 1 h, $CH_2Cl_2$/MeOH [1 : 1], 0 °C, then 25 °C, 0.5 h, 86%; m. 2.0 equiv. of $SO_3$·*pyr.*, 10.0 equiv. of DMSO, 5.0 equiv. of $Et_3N$, $CH_2Cl_2$, 25 °C, 0.5 h, 82%; n. 3.0 equiv. of LDA, THF, 0 °C, 0.25 h; then 1.2 equiv. of 18 in THF, −78 to −40 °C, 0.5 h, then 1.0 equiv. of 17 in THF at −78 °C, high yield of 19 and its 6*S*,7*R*-diastereomer (*ca.* 1 : 1 ratio); o. 3.0 equiv. of TBSOTf, 5.0 equiv. of 2,6-lutidine, $CH_2Cl_2$, 0 °C, 2 h; p. 2.0 equiv. of $K_2CO_3$, MeOH, 25 °C, 15 min, 31% of 21 and 30% of its 6*S*,7*R*-diastereomer from 17; q. 6.0 equiv. of TBAF, THF, 25 °C, 8 h, 78%; r. 5 equiv. of 2,4,6-trichlorobenzoylchloride, 6.0 equiv. of $Et_3N$, THF, 25 °C, 15 min, then add to a [illegible] .0 equiv. of 4-DMAP in toluen [illegible] M based on 22), 25 °C, 0.5 h, 90%; s. 20% $CF_3COOH$ [by volume] in $CH_2Cl_2$, 0 °C, 1 h, 92%. LDA = lithium diisopropylamide; 4-DMAP = 4-dimethylaminopyridine; TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium hexamethyldisilylamide; DMSO = dimethylsulfoxide; Tf = triflate.

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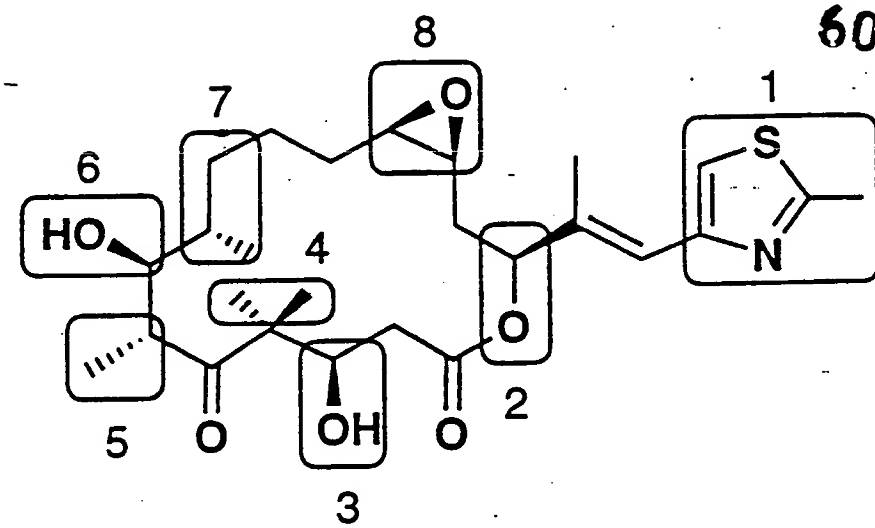
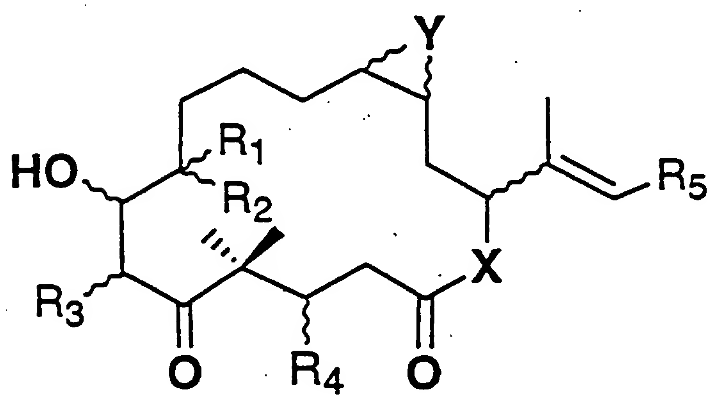
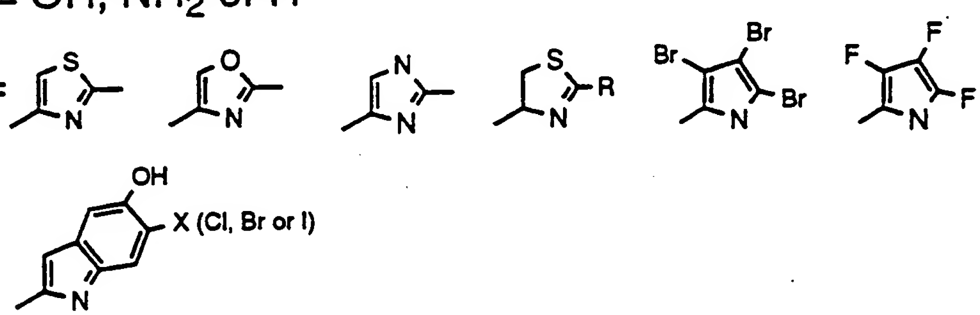




$R_1$= Me, Et or H
$R_2$= Me, Et or H
$R_3$ = Me, Et, or MeOR
$R_4$ = OH, $NH_2$ or H

$R_5$=




X = O, NH
Y = O, N, $CH_2$

FIGURE 1

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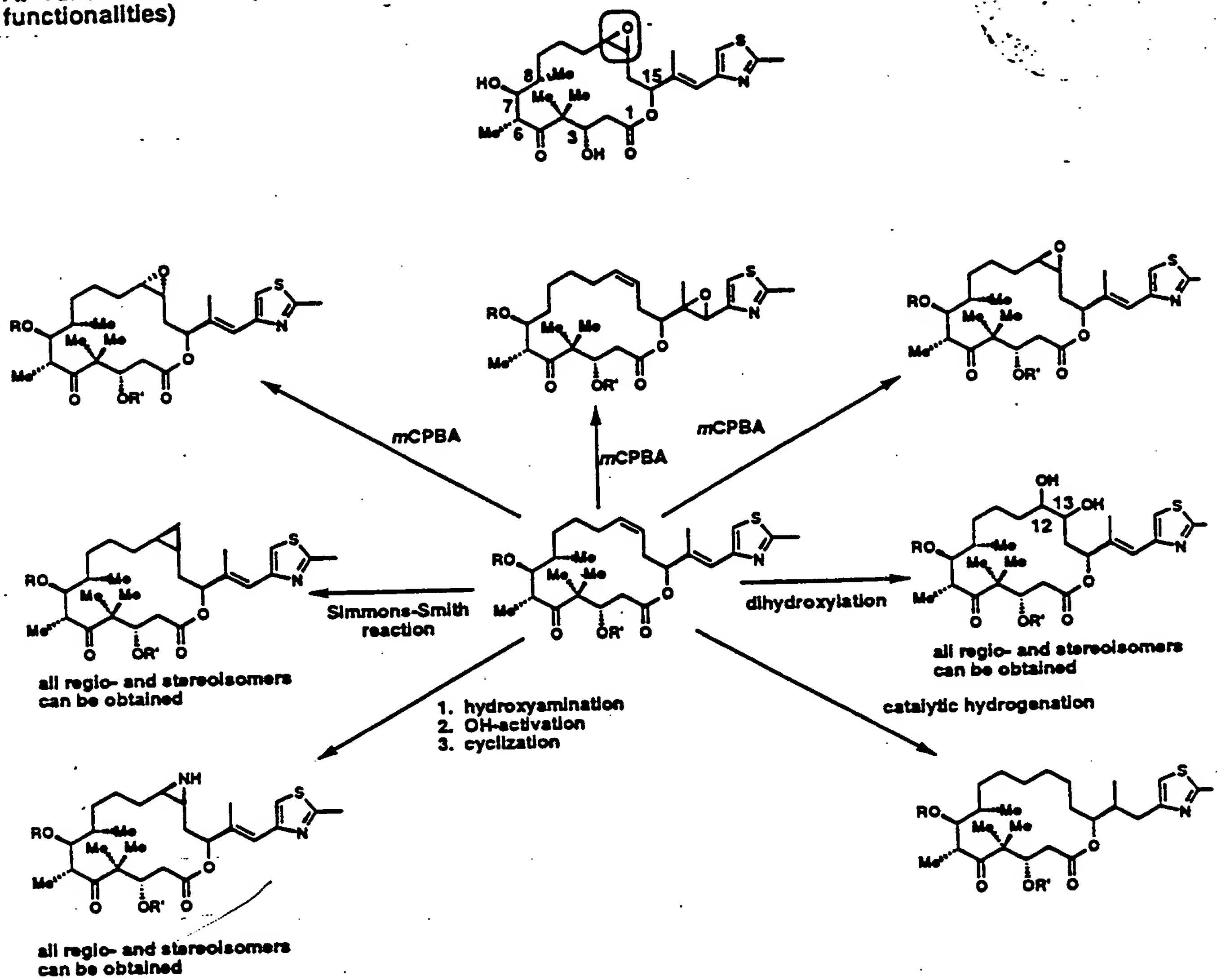
A. Variations of the epoxide functionality (stereoisomers, regioisomers, other functionalities)




R is selected from the group consisting of H, methyl, n-alkyl, acyl, allyl, benzyl.

FIGURE 2

Variation of the side chain

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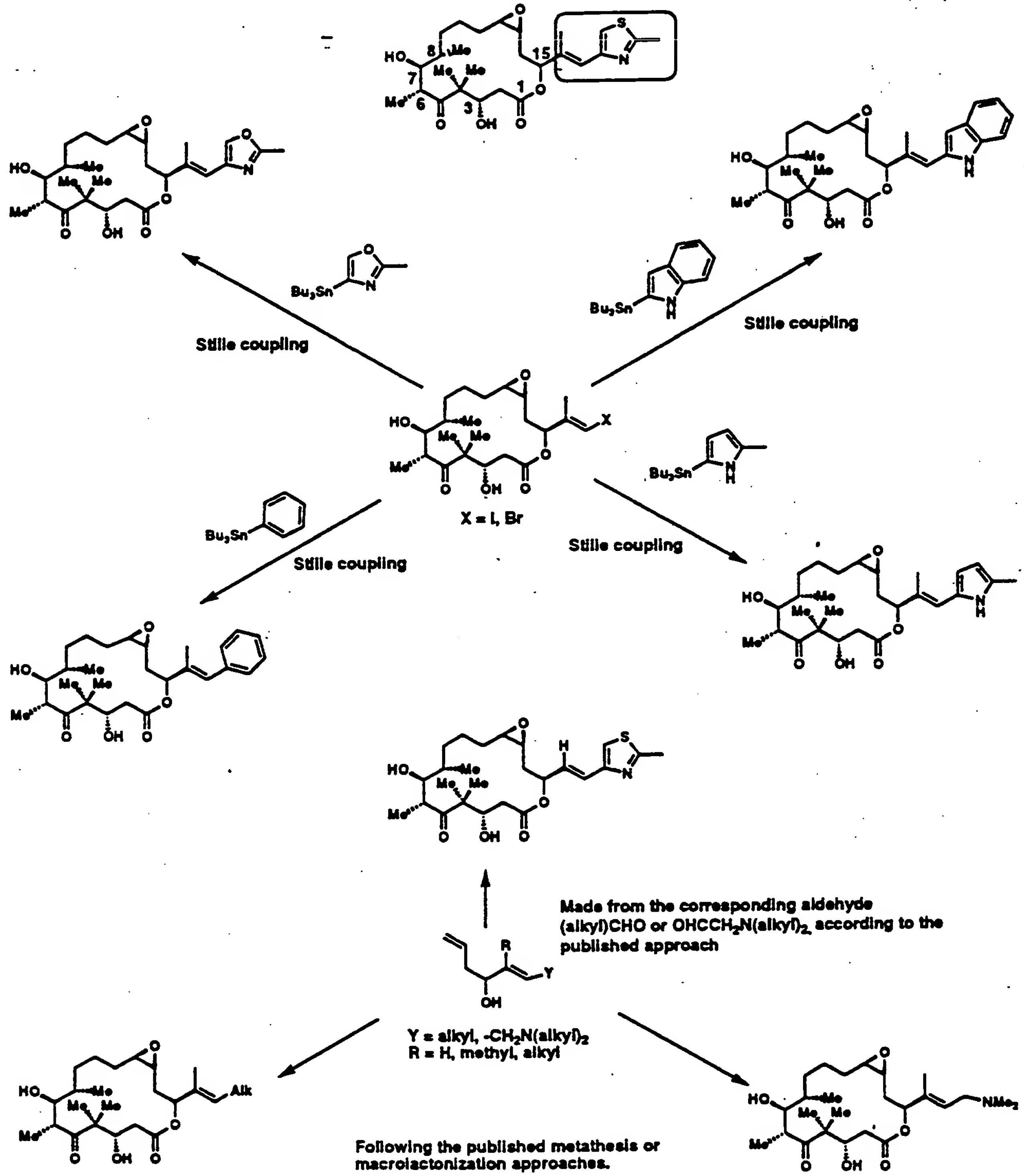


FIGURE 3

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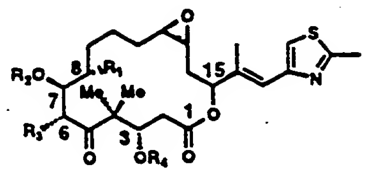
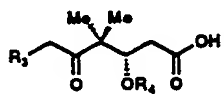
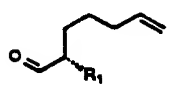
C. Synthesis of all possible stereoisomers at carbons 3, 5, 7, 8 and 15.



All different isomers can be obtained by the established route.
$R_2$, $R_4$ = H, Me, n-Alkyl, Silyl, Benzyl
$R_1$, $R_3$ = H, n-Alkyl



made from different acyl chlorides by the published procedure



synthesized by Oppolzer's protocol as the original α-methyl aldehyde

FIGURE 4

D. Variations of the gem-dimethyl functionality

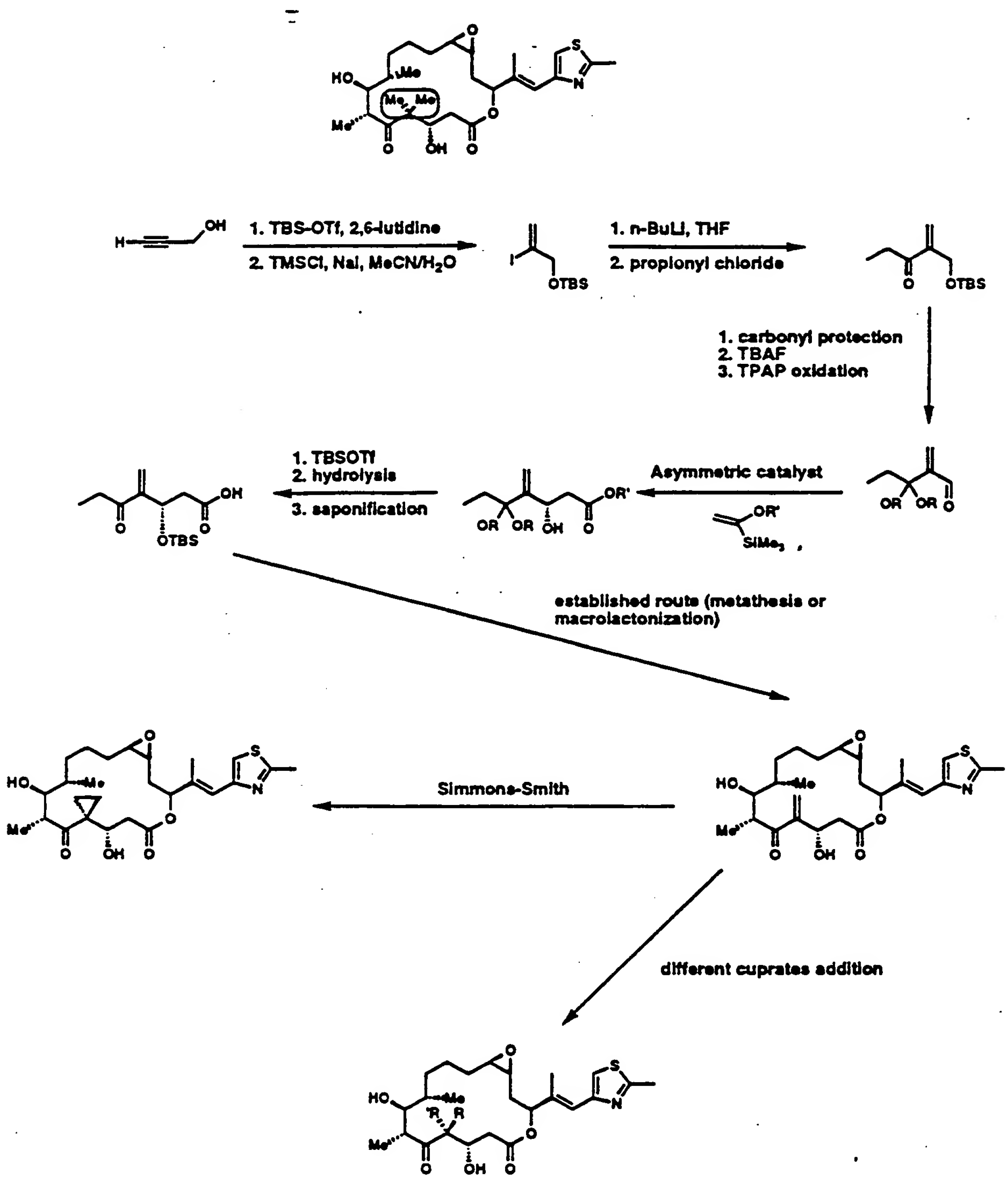



FIGURE 5

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E. Variations of the ring side

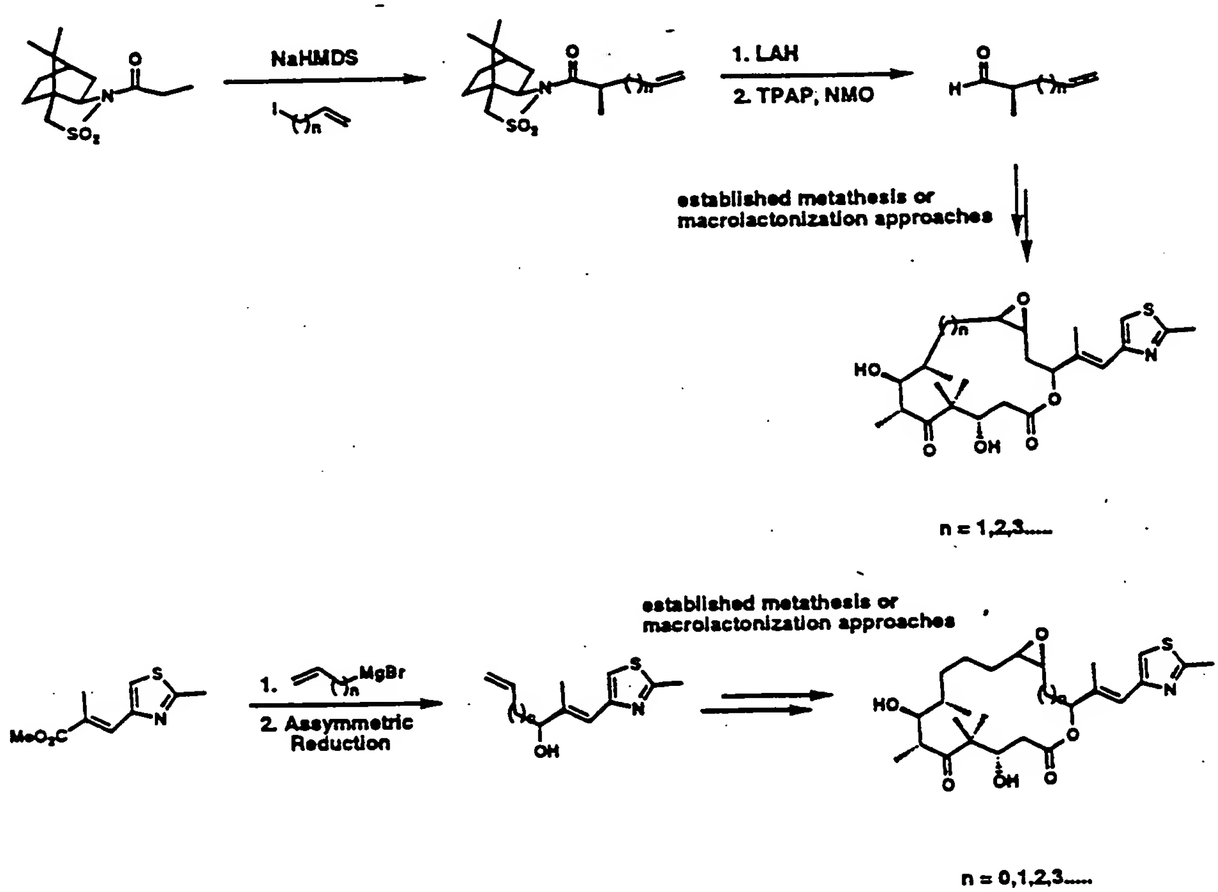


FIGURE 6

F. Generation of epothilone-taxoids hybrids

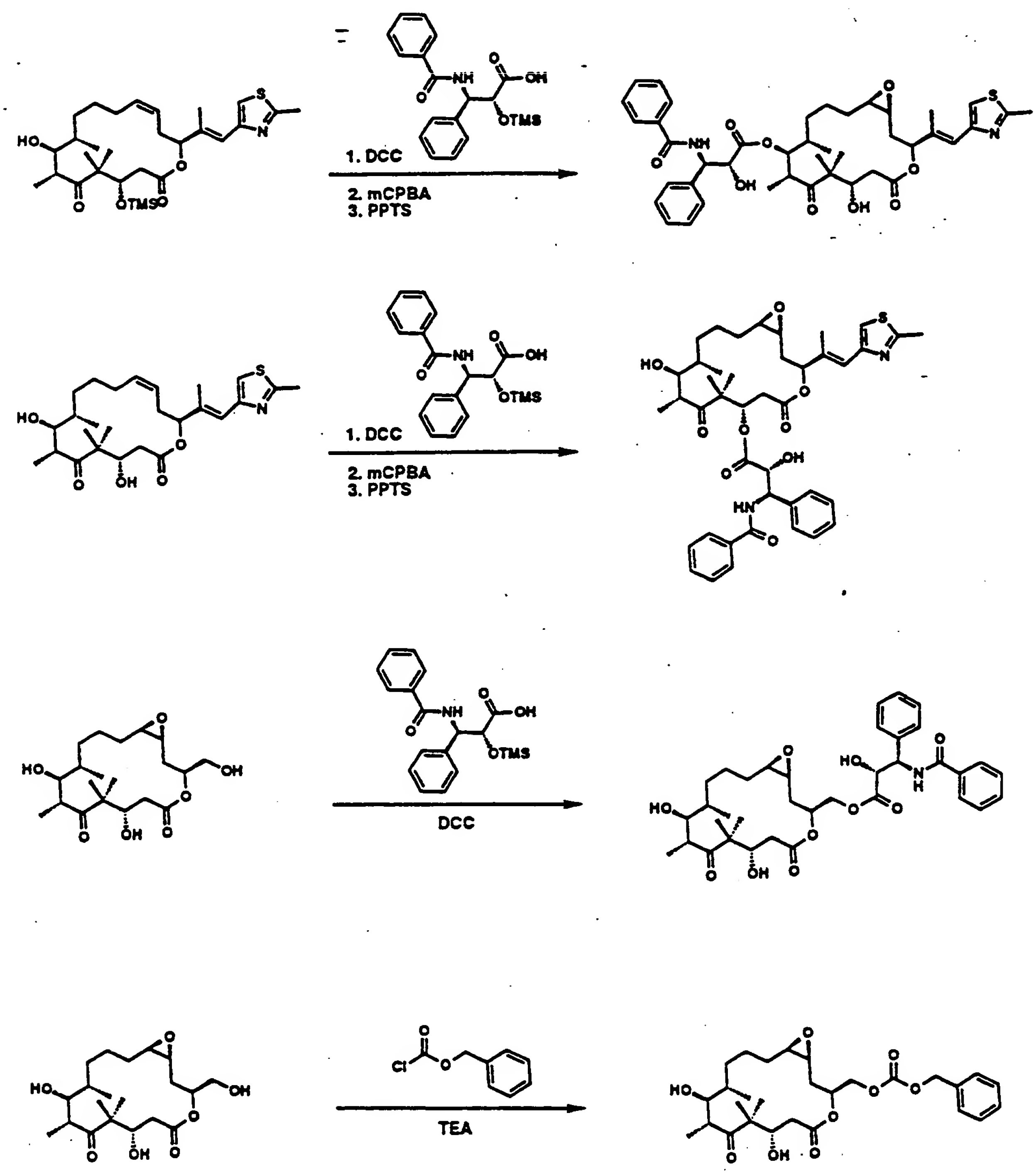


Figure 7